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13. ABSTRACT (Maximum 200 words)

Tomosynthesis is a method of obtaining tomographic images of the breast. We have developed a mthod for breast tomosynthesis using a full-field digital mammography system. Algorithms have been developed to reconstruct any plane in the breast from a series of low-dose images obtained as the x-ray source moves in an arc above the breast. Our results indicate: 1) a radiation dose similar to a conventional mammogram may be used for tomosynthesis, 2) the optimum number of view is seven to nine based on the trade-off between total exposure time and the number of views, and 3) the optimum tomosgraphic angle is 30 to 40 degrees. Finally, we have developed a number of phantoms for basic image quality measurements and complex phantoms for an observer study. Our results indicate tomosynthesis will over improvements over conventional breast screening methods.

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Annual Report

Tomosynthesis Breast Imaging: Early Detection and Characterization of Breast Cancer

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Introduction

Despite recent advances in mammography imaging, it has been shown that many cancers are missed by mammography [1-4]. One of the main reasons cancers are missed is that they are masked by radiographically dense fibroglandular breast tissue which may be overlying or encompassing the cancer [5-11]. Standard mammography techniques, either analog (film) or digital, suffer from the limitation that despite breast compression, three-dimensional anatomical information is projected onto a two-dimensional detector. Tomosynthesis is a technique that allows the radiologist to view individual planes of the breast, potentially reducing the problem of superimposed structures that may limit conventional mammography techniques.

TOMOSYNTHESIS

Conventional tomography preceded computed tomography and was preformed by moving the x-ray tube through a limited arc to blur structures above or below a selected plane of interest. Conventional tomography provides an image of a *single* tomographic plane for each movement of the x-ray source. Features in only one plane of the image remain in sharp focus while projections of features from all other planes are blurred. Multiple focal planes or slices require much higher doses. Tomosynthesis, however, utilizes a digital detector and acquisition system to provide images of *multiple* planes from a single movement of the x-ray source. This is accomplished at a *total* dose approximately equal to that of a single mammographic view. Conventional film-screen tomography is usually accomplished either in the Twinning method (Figure 1), in which the x-ray tube and detector are moved in a linear path on opposite sides of the patient, or the Grossman method, in which the motion occurs in an arc on opposite sides of the patient. We have developed a method for digital tomosynthesis breast imaging where the x-ray tube is moved in an arc above the stationary breast and digital detector [12] as shown in Figure 2. By shifting and adding the digital images, it is possible to reconstruct *any* plane in the breast that is parallel to the detector. This

technique can provide a series of images encompassing the entire breast, with each image displaying only one plane of the breast in sharp focus.

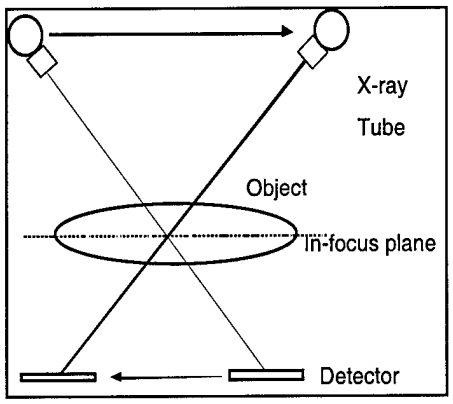

Figure 1. Conventional linear tomography using the Twinning Geometry.

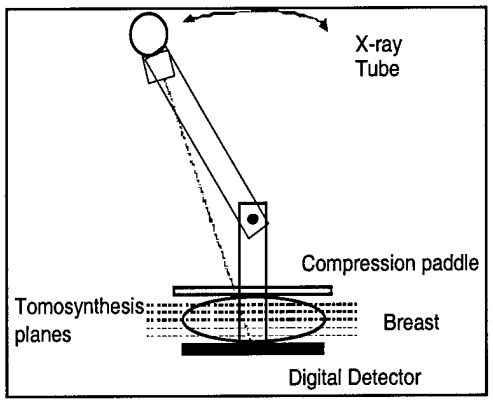

Figure 2. Proposed geometry for breast tomosynthesis.

Several authors [13-15] have demonstrated the use of tomosynthesis with film as a detector, based on the earlier work of Ziedes des Plantes [16]. Although these studies demonstrated that it was possible to use film as a detector, the system was much too complicated for routine clinical use. Miller et al. concluded that in general, images must be obtained from at least eight angles to obtain a high-quality tomosynthesis image [13]. Electronic image acquisition using an image intensifier as a detector and an analog-to-digital converter to obtain digital images from multiple angles has been used in numerous studies outside mammography [17-25]. Unfortunately, the use of an image intensifier with a curved detector surface has limited the success of all of these previous attempts at digital tomosynthesis.

Clinical application of breast tomosynthesis has been delayed by the lack of a full field flat digital detector with rapid readout time. The full field digital mammography system installed at our institution is ideally suited for breast tomosynthesis because of the following properties: 1) low noise, 2) high resolution, 3) large flat detector area with minimal image distortion, and 4) rapid image readout times.

The goals of the first year of this grant were to:

- Develop reconstruction algorithms
- Optimize the technical parameters
- Develop phantoms for image quality and detection tasks.

Body

Methods

Our current method for tomosynthesis imaging utilizes a flat-panel digital mammography system that has low noise and a 300-millisecond image readout time. Images are obtained as the x-ray tube moves in an arc above the breast. X-ray tube motion is manual and a precision inclinometer and fiducial marks are used for angle and x-ray tube position determination.

This system requires different image reconstruction algorithms than used in previous systems, which were based on either the Twinning method or the Grossman method. A complete derivation of the image reconstruction algorithms for our geometry is contained in reference [12]. Algorithm development will be discussed. Optimizing the techniques for digital breast tomosynthesis have involved three primary technical variables. These variables are 1) radiation dose, 2) total tomographic angle and 3) the number of images. These variables will be primary determinants of tomosynthesis image quality. Discussed below are the results of parameter optimization and phantom development.

Algorithm Development

We have modified our early algorithms to increase the speed of image reconstruction. Current algorithms are written in MATLAB software and will reconstruct a tomosynthesis plane in approximately one minute. This compares to approximately ten minutes per image for the early algorithms. We are also investigating several methods of removing the contribution of out of plane structures. In addition to using methods previously described in the literature, we are collaborating with several researchers to remove the out of plane structures from the reconstructed image.

The removal of linear streaking artifacts is shown in Figure 9C of the paper "Digital Tomosynthesis in Breast Imaging" included in the appendix.

Optimization of Image Acquisition Parameters

RADIATION DOSE

The radiation dose needed for tomosynthesis depends upon a number of factors. First, since tomosynthesis involves acquiring a number of low dose images, system or electronic noise in the detector and read-out electronics is critical. For example, if a tomosynthesis data set consists of eight images with the total dose equal to a conventional single view mammogram, then each image would have to be obtained at approximately one eighth the radiation dose of a conventional mammogram. One advantage of tomosynthesis is that the x-ray or quantum noise

in the final reconstructed image is determined by summing all of the images and thus by the total radiation dose. However, for low dose images it is possible that electronic noise may be a substantial fraction of the total noise. Therefore, for tomosynthesis a low noise detector is essential and the detector should be quantum limited even at doses which may be 10 to 20% of the dose of a conventional mammogram.

Another issue for radiation dose in tomosynthesis is the angle of the projections. For example, at an angle of 20 degrees from the normal to the detector the effective breast thickness is increased by about 5%. Thus, a slightly higher dose may be needed for large angles to keep the noise of these images similar to those obtained near at zero degrees.

Results indicate that a radiation dose of one to 1.5 times higher than conventional mammography will provide high quality tomosynthesis images and distributing the dose with slightly higher exposures at the start and finish of the tube arc will result in improved tomographic images.

TOMOGRAPHIC ANGLE

The total tomographic angle or the total arc used for the x-ray tube motion will effect image quality. The thickness of the in-focus plane in the direction perpendicular to the detector is inversely related to the total angle used. From an image quality standpoint, a larger angle creates more misregistration of objects above and below the plane of interest that is beneficial. This will result in more spread of the out-of plane structures and improve the overall image. The trade-off is in the total number of images that may need to be viewed. For example, if the total tomographic arc is 40 degrees the in-focus plane thickness is approximately 2 mm. For a tomographic angle of 20 degrees the in-focus plane would be about 4 mm. Thus for a larger angle, image quality may be improved but at the cost of having to reconstruct and view twice as many images.

For large angles beyond ±20 degrees several other issues arise, including the increased breast thickness which must be transversed at steep angles, and the possibility that some of the breast tissue will not appear on the detector. Our results indicate a tomographic angle of 30 to 40 degrees is appropriate.

NUMBER OF IMAGES

The next technical parameter that must be considered is the total number of images that will be acquired. As mentioned earlier if a very large number of images are acquired the possibility of electronic noise becoming a major noise source in the image is increased. There are also image quality issues. First more images provides more complete blurring of out-of-plane structures and a reduction in the amount of high frequency information form out-of-plane structures.

The other major consideration is the total imaging time and how patient motion is affected. Our initial experience indicates that seven to ten images will be required at a total dose approximately equal to a conventional mammogram. For seven to ten images, each exposure would be approximately 100 to 200 milliseconds plus a 300-millisecond readout time. If the x-ray source motion takes place during the 300-millisecond image readout time, total image acquisition time would be three to five seconds. This length of time is common for magnification views, and patient motion is not expected to be a major problem.

Phantom Development

We have developed a new image quality phantom specifically for the purpose of evaluating tomosynthesis images. This phantom contains two fine wires (20 micron thick) at 7 degrees and 20 degrees to evaluate the modulation transfer function of tomosynthesis. In addition, the phantom contains structures at different levels to evaluate the ability of tomosynthesis to blur out of plane structures. This phantom was constructed by CIRS (Computerized Image Reference Systems, Norfolk, VA) using a 5-cm thick phantom of BR12 breast equivalent material.

The results with this phantom indicate the blurring increases with increasing tomographic angle as predicted. The amount of blur is also similar to conventional tomography for comparable tomographic arc. The blur is not as uniform as conventional tomography because the tube motion is a step and expose rather than the continuous tube motion used in conventional tomography.

Images of an ACR phantom indicate that small objects are still detectable with tomosynthesis including the third spec group in the ACR phantom at doses comparable to conventional mammography. The MTF is slightly degraded in the in-focus plane compared to a conventional digital image using the same detector, however, because the tube is not moving during exposures the MTF is higher than that for conventional tomography.

Complex phantom development is underway. These phantoms will be used in the second year of the study for an observer study. We are investigating two types of phantoms and have had several prototypes constructed by CIRS. These phantoms will contain simulated fat, glandular and disease (masses and microcalcification clusters).

Conclusions

The potential advantages of tomosynthesis compared to conventional mammography are outlined below.

INCREASED SENSITIVITY, AND IMPROVED ABILITY TO DETECT CANCERS IN DENSE BREAST TISSUE

Tomosynthesis may prove to be a valuable screening tool for women with dense breasts. The ability to "see into the middle" of the breast by blurring the superimposed structures will potentially allow significant improvements in the sensitivity of mammography screening.

INCREASED SPECIFICITY AND ABILITY TO CHARACTERIZE A LESION

Current mammographic techniques have poor specificity; in the United States 70-90% of all breast biopsies are negatives [26-28]. Tomosynthesis will provide the radiologist with an improved image of a potential lesion by blurring the structures above and below the lesion. This may allow the radiologist to have improved confidence in lesion classification and decrease the fraction of negative biopsies. The improved visualization of lesion borders may also display spiculations that are characteristic of malignant lesions. It may be possible to perform the diagnostic evaluation of a lesion with tomosynthesis, thus reducing the radiation total radiation exposure compared to a standard diagnostic examination, which may involve up to ten mammograms. This would save time and reduce patient radiation exposure.

IMPROVED DISCRIMINATION OF SUPERIMPOSED STRUCTURES FROM BREAST CANCER

Many women who are called back for additional evaluations after mammography screening are recalled because normal breast structures may superimpose and mimic a breast cancer [26]. A set of tomosynthesis images may be used to discriminate between superimposed tissues and real masses, thus eliminating these unnecessary callbacks. These unnecessary callbacks lead to higher health care costs and also to significant anxiety for women and their families. Tomosynthesis will also provide three-dimensional information concerning the dimensions of a lesion, whether microcalcifications are associated with a mass, and how they are distributed. The three dimensional distribution of calcifications is thought to be a useful indicator in discriminating benign versus malignant lesions [29].

DECREASED BREAST COMPRESSION

In conventional mammography firm breast compression is important to spread normal breast anatomy to improve the detection of lesions. In tomosynthesis, it may be possible to use less compression, since blurring of out-of-plane structures (breast structures that are above or below the plane of interest) actually increases with less compression. Limited compression will still be required to minimize patient motion.

In summary, the proposed tomosynthesis method has several unique features that include a stationary detector and a x-ray tube that moves in an arc above the

breast. This geometry has several advantages: 1) there are no moving parts near the breast or abdomen, 2) existing mammography machines may be easily altered to allow this type of motion since many already provide the ability for the x-ray tube to move in an arc above the breast and 3) a unit modified to do tomosynthesis imaging using this design will still be completely usable for routine breast imaging. A dedicated tomosynthesis system is not required.

The work done in the first year of this grant has laid the groundwork for the continued development and testing of Breast tomosynthesis. This project will perform observer studies in the next year to verify the clinical benefits of breast tomosynthesis. Algorithm, parameter optimization and phantom development have been completed or near completion. The investigators have published three papers on breast tomosynthesis in the first year of the grant. The proceeding article from the Nijmegen, Netherlands conference – The International Digital Mammography Workshop was used as the basis of this report since it was reporting on the technical progress. The other two articles are attached.

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Appendices – Publications included:

Digital Tomosynthesis for Breast Imaging – Loren Niklason, Bradley Christian, Laura Niklason, Daniel Kopans et al, Radiology, 1997: 205:399-406.

Digital Breast Imaging: Tomosynthesis and Digital Mammography – Loren Niklason, Daniel Kopans and Leena Hamberg – in press Breast Disease

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Digital Tomosynthesis in Breast Imaging[1]

PURPOSE: **To describe and evaluate a method of tomosynthesis breast imaging with a full-field digital mammographic system.**

MATERIALS AND METHODS: **In this tomosynthesis method, low-radiation-dose images were acquired as the x-ray source was moved in an arc above the stationary breast and digital detector. A step-and-expose method of imaging was used. Breast tomosynthesis and conventional images of two imaging phantoms and four mastectomy specimens were obtained. Three experienced readers scored the relative lesion visibility, lesion margin visibility, and confidence in the classification of six lesions.**

RESULTS: **Tomosynthesis image-reconstruction algorithms allow tomographic imaging of the entire breast from a single arc of the x-ray source and at a radiation dose comparable with that in single-view mammography. Except for images of a large mass in a fatty breast, the tomosynthesis images were superior to the conventional images.**

CONCLUSION: **Digital mammographic systems make breast tomosynthesis possible. Tomosynthesis may improve the specificity of mammography with improved lesion margin visibility and may improve early breast cancer detection, especially in women with radiographically dense breasts.**

THE best method of detecting early stage breast cancer is mammography (1). It has been shown that finding breast cancer in its early stages saves lives (2). Even with the recent advances in mammographic imaging, 10%–30% of breast cancers may be missed, and other cancers are not detected early enough to make a cure possible (3–7). The main reason that breast cancers are missed is that the cancer is often obscured by radiographically dense, fibroglandular breast tissue (8–14). Holland and colleagues (8) found that 76% of missed cancers were in dense breasts.

This article describes a tomosynthesis method that allows the radiologist to see through the "structured noise" of normal breast tissue to improve the detection and characterization of early breast cancer. In conventional screen-film tomography, the x-ray source and the screen-film detector move in opposite directions, so that only features in one plane of the image remain in sharp focus. In tomography, one exposure is necessary for each imaged plane. One of two tomographic methods is typically used: the Twinning method (Fig 1) or the Grossman method (Fig 2). In the tomosynthesis method proposed here (Fig 3), multiple images are acquired as the x-ray tube is moved in an arc above the stationary breast and detector. The radiation dose is low for the acquisition of images at each angle, and the total radiation dose for the acquisition of all of the images is equivalent to or slightly higher than the dose in standard single-view mammography. By shifting and adding the digital images, it is possible to reconstruct any plane in the breast that is parallel to the detector. This technique can provide a series of images of the entire breast, with each image displaying only one plane of the breast in sharp focus.

Several authors (15–17) have demonstrated tomosynthesis with film as a detector by using the methods derived by Ziedses des Plantes (18). Miller and colleagues (15) concluded that, in general, images must be obtained from at least eight angles to produce a high-quality tomosynthesis image. Although these authors demonstrated that it was possible to use film as a detector, the system was too complicated for routine clinical use.

Electronic image acquisition has been performed by using an image intensifier as a detector and an analog-to-digital converter to obtain digital images from multiple angles in numerous applications of tomosyn-

Index terms: Breast neoplasms, radiography, 00.30, 00.121 • Breast radiography, radiation dose, 00.121 • Breast radiography, technology, 00.121 • Radiography, digital, 00.121 • Radiography, technology, 00.121

Abbreviation: ACR = American College of Radiology.

Radiology 1997; 205:399–406

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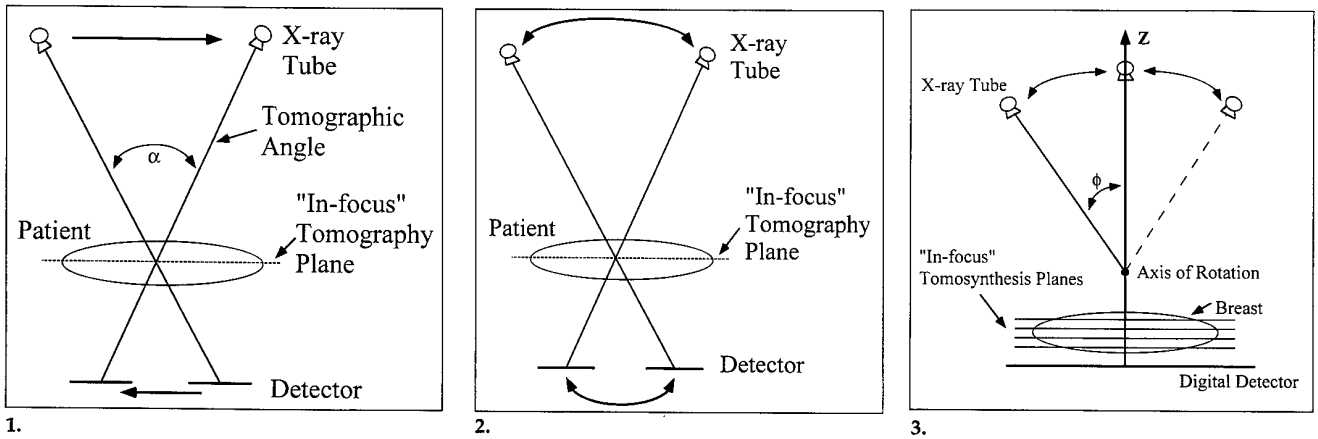
Patent applied for by Massachusetts General Hospital, Boston.



Figures 1–3. **(1)** Twinning geometry for tomographic imaging. The x-ray source and detector move parallel to the in-focus tomographic plane. α = tomographic angle. **(2)** Grossman geometry for tomographic imaging. The x-ray source and detector move in an arc. **(3)** Proposed geometry for breast tomosynthesis. The x-ray source is stationary during each x-ray exposure and is then moved along an arc above the breast to the next position. The number of positions is variable. The breast and digital detector remain stationary. Z = distance above the digital detector, ϕ = x-ray–source angle.

thesis outside of mammography (19–27). Both linear and circular x-ray–tube motions have been investigated. The feasibility of tomosynthesis has been demonstrated in angiography (20–22,24,26). Tomosynthesis has also been investigated in tomography of the lung (20) and the ear (27) and in knee arthrography (20). Images superior to conventional tomograms have been obtained by reducing the streak artifacts by means of one-dimensional filtering of the linear tomosynthesis images (19,27–29). Chakraborty and colleagues (27) have suggested a one-dimensional, unsharp masking technique called self-masking tomosynthesis. Additional methods to reduce the contribution of out-of-focus structures to the in-focus plane have been explored (30–32). Unfortunately, the use of an image intensifier with a curved detector surface has limited the success of these previous attempts at digital tomosynthesis.

Despite numerous studies that have explored the use of tomosynthesis, successful clinical application has been delayed by the lack of a full-field, flat, digital detector with rapid readout. Digital imaging technology has now been introduced that makes tomosynthesis imaging of the breast practical in a clinical setting. The full-field, digital mammographic system undergoing clinical evaluation at our institution is ideally suited for the clinical application of tomosynthesis because of the following properties: low noise; large, flat surface area with minimal image distortion; and rapid image readout.

The proposed method of tomosynthesis was developed at our institution and represents an extension of the technology described in earlier reports. The main differences between this and previous studies are primarily the use of a stationary detector and of existing mechanical arm systems that translate the x-ray tube in an arc above the detector. We have derived reconstruction methods to allow tomosynthesis image reconstruction for this geometry. We believe that tomosynthesis has the potential to improve current mammographic imaging by increasing the sensitivity and specificity in the detection of breast carcinoma. Thus, we performed this study to describe and evaluate a method of tomosynthesis breast imaging with a full-field digital mammographic system.

MATERIALS AND METHODS

A schematic of the mammographic system used for digital breast tomosynthesis is shown in Figure 4. The basic system is a mammographic system (model DMR; GE Medical Systems, Milwaukee, Wis) with a full-field digital image receptor. The system has been modified to allow imaging at any angle up to ±27° from the perpendicular to the detector. As shown in Figure 4, the x-ray source pivots about a point above the detector. The x-ray source is stationary during the exposure and then is manually moved to the next position before the next image is obtained.

The digital detector is composed of cesium iodide phosphor on an amorphous silicon transistor-photodiode array. This detector was developed by General Electric Corporate Research and Development (Schenectady, NY). The pixel pitch is 100 μm and the image readout time is 300 msec. The tomosynthesis images were obtained without an antiscatter grid to avoid grid cutoff for the angled projections. The x-ray–source angle (ϕ in Fig 3) was determined with a precision inclinometer (model 02538-01; Lucas Control System Products, Hampton, Va) with a range of ±20° and an accuracy of ±0.1° for 0°–10° and of ±1% for 10°–20°.

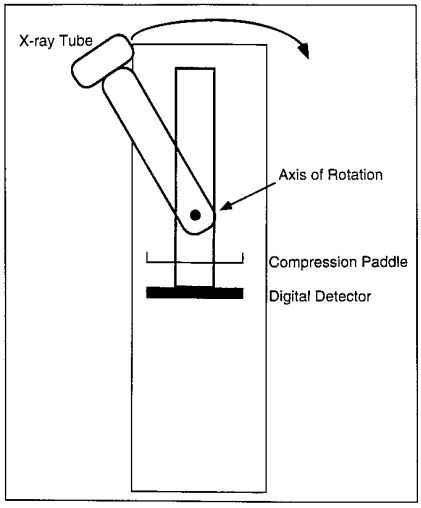


Figure 4. Mammographic system used for tomosynthesis. The x-ray tube is on a rigid mechanical arm that pivots about a point above the breast.

The tomosynthesis projection images were obtained at discrete x-ray–source positions as the tube was moved above the breast, as shown in Figure 5. For simplicity, only four x-ray–source positions are shown in Figure 5; however, the number of x-ray–source positions is variable. The tomosynthesis images in any plane in the breast may be reconstructed by using the method shown. The projection images from x-ray–source positions 1–4 were transformed, as described in the Appendix, to simulate images obtained from x-ray–source positions 1a–4a (Fig 5). After transformation of the images, the geometry is similar to Twinning geometry, except that the detector does not move. De-

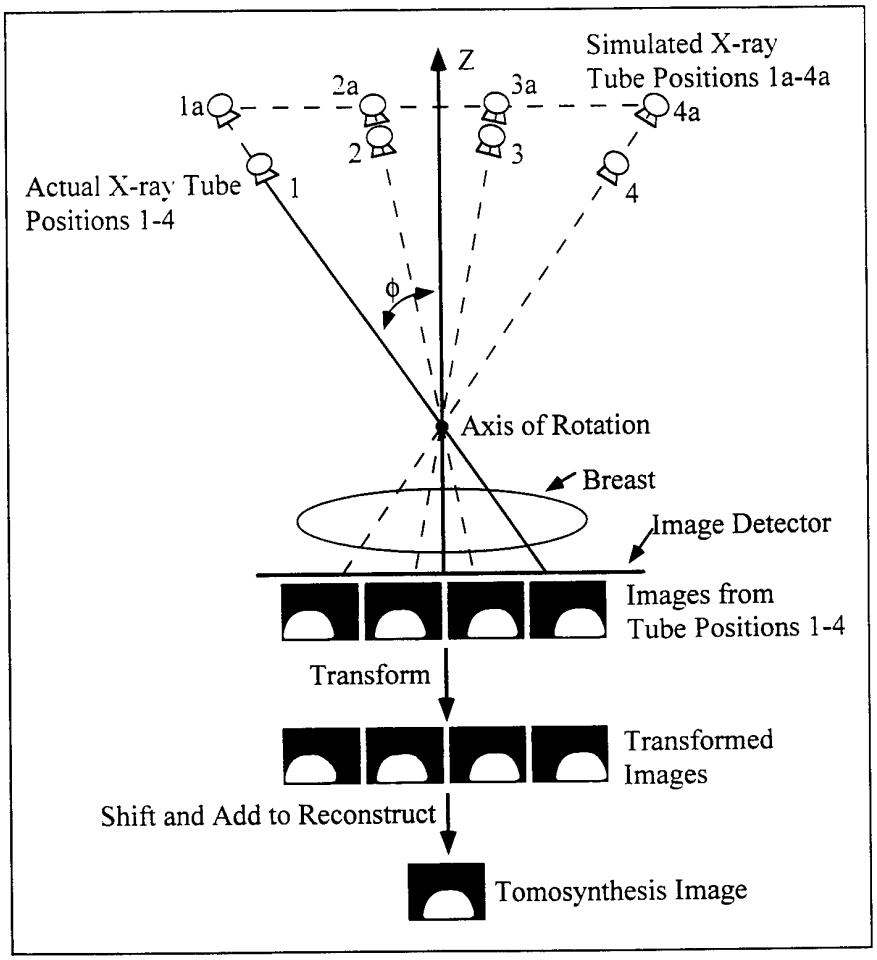


Figure 5. Tomosynthesis reconstruction method with four x-ray–tube positions shown. Images are obtained from positions 1–4 and are transformed, by using the algorithms described in the Appendix, to construct images that would be obtained from source positions 1a–4a. These images simulate tomographic images obtained by using Twinning geometry and may be shifted and combined to create a tomosynthesis image at any level in the breast. Z = distance above the digital detector, ϕ = x-ray–source angle.

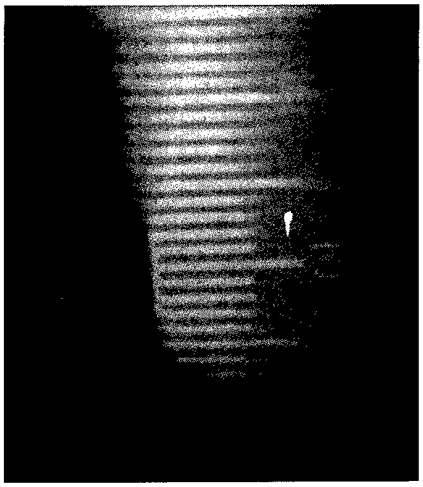


Figure 6. Tomosynthesis image of a Picker tomographic phantom reconstructed at 3 cm above the detector platform demonstrates the thickness of the in-focus plane for the tube motion.

tector motion is simulated by shifting the images in the computer. The transformation and shifting algorithms may be repeated to reconstruct the tomographic planes at any height above the detector. The mathematic reconstruction algorithms are derived in the Appendix.

Images were obtained in one of two tomographic phantoms (one made by Picker International, Cleveland, Ohio, and the other the accreditation phantom of the American College of Radiology [ACR], Reston, Va). The tomosynthesis images of both phantoms were obtained with the following parameters: 26 kVp, molybdenum filter, molybdenum target, 20 mAs per view, and nine views at −20°, −15°, −10°, −5°, 0°, 5°, 10°, 15°, and 20° from the detector perpendicular. A conventional screen-film image of the ACR phantom was obtained at 26 kVp and 126 mAs with a molybdenum target and a molybdenum filter. The total mean glandular radiation dose for the tomosynthesis images was 1.4 times that for the conventional screen-film images. A conventional digital image of the ACR phantom also was obtained by using the same technique as in screen-film imaging, except that 120 mAs was used. Radiation dose estimates for the tomosynthesis projection images, compared to those for the conventional images, take into account differences in the source-to-object distance and in the x-ray–path length through the object.

Images of four unfixed mastectomy specimens were obtained. The specimens were placed in a polymerized methyl methacrylate box and compressed by using a movable top plate. Tomosynthesis specimen images were obtained at seven to nine projections and with a total tomographic angle of 30°–40°. The total radiation dose was varied 0.89–1.74 times that in conventional mammography in the same specimen. Tomosynthesis images of the specimens were reconstructed on a workstation (Sparc 20; Sun Microsystems, Mountain View, Calif). After the initial images were acquired for each angle, we reconstructed tomographic images at 1.5–3.0-mm spacing to display in-focus tomosynthesis images of the entire breast.

Conventional screen-film mammograms were obtained with film (MR5II; Agfa, Ridgefield Park, NJ) and screens (MR detail; Agfa) by using extended processing. These images were obtained with automatic exposure control by using a conventional screen-film system. The kilovolt peak, focal spot sizes, radiation output, and half-value layers of this unit were all closely matched to those of the digital unit.

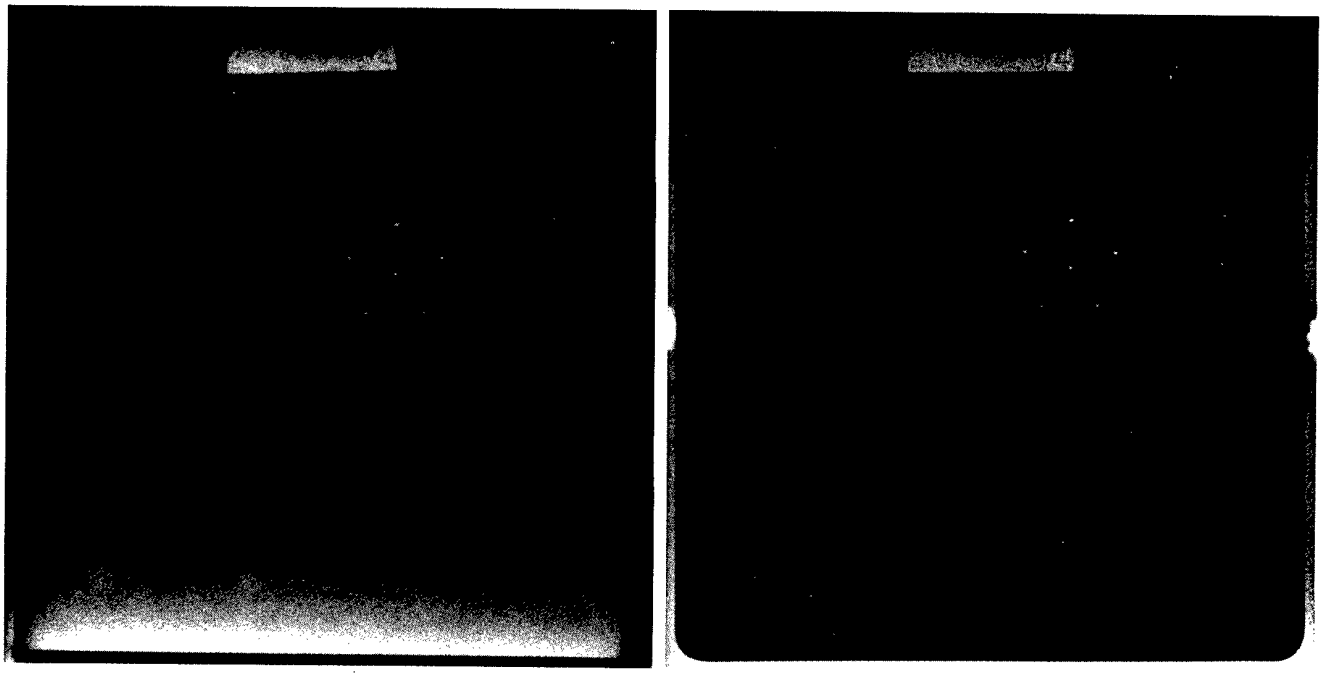
The two units were installed in the same room, and adjustments were made to match the above parameters during installation. A molybdenum target and a molybdenum filter were used to obtain all of the specimen images, which included the digital, tomosynthesis, and screen-film images.

A preliminary reader study was performed to compare tomosynthesis images with screen-film images of all lesions in the specimens. The conventional screen-film image was shown next to the tomographic image that best demonstrated the mass or calcification in each specimen on a standard, high-intensity, mammographic view box. The digital tomosynthesis images were printed by using a laser imager (40 μm pixel size; Agfa).

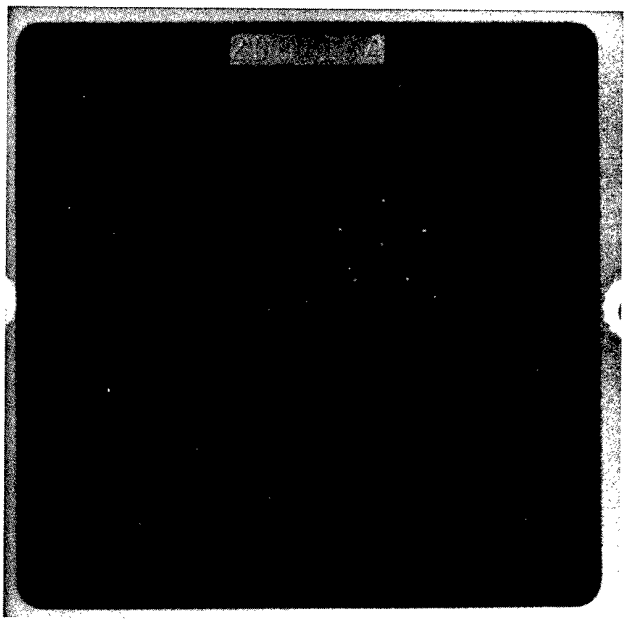
Three board-certified radiologists (D.B.K., P.J.S., A.A.G.) with special expertise in mammography were asked to compare the visibility of a mass or a cluster of calcifications in each specimen. Before reading, the location of the lesion was identified by an expert reader (D.B.K.) and marked with an arrow. The readers scored the lesion visibility, lesion margin visibility, and confidence in the classification of benign versus malignant lesions. Scoring was based on a five-point scale: (*a*) conventional images were diagnostically superior, (*b*) conventional images were superior, (*c*) conventional and tomosynthesis images were equal, (*d*) tomosynthesis images were superior, and (*e*) tomosynthesis images were diagnostically superior.

RESULTS

Figure 6 is a tomosynthesis image obtained in a tomography phantom



a. b.



c.

Figure 7. Images of the ACR phantom. **(a)** Digital tomosynthesis image. **(b)** Conventional digital image. **(c)** Screen-film image.

reconstructed to have an in-focus plane at 3 cm above the detector platform. This figure demonstrates the thickness of the in-focus plane. This image was obtained at a total tomosynthesis angle ($2 \times \phi$ in Fig 3) of 40°. This 40° tomosynthesis angle is equivalent to a tomographic angle of 29.4° (α in Fig 1) in conventional linear tomography for an in-focus plane at 3 cm above the detector platform. The in-focus plane thickness would be expected to be 2.5 mm for this tomographic angle according to conventional geometry (33). This calculated in-focus plane thickness agrees well with that in the tomosynthesis image (Fig 6).

Images of an ACR phantom obtained by using tomosynthesis, conventional screen-film imaging, and conventional digital imaging are shown in Figure 7. The tomosynthesis image of the ACR phantom was reconstructed at the level of the targets. The masses and fibers are seen as well with tomosynthesis as with conventional digital imaging. The fourth calcification group is seen with tomosynthesis, but not as clearly as with conventional imaging. The borders of the calcifications are not as sharp on the tomosynthesis image as they are on the conventional images, because the tomosynthesis image is the summation of nine different projections. Nonetheless, the image quality of the tomosynthesis image is sufficient to pass the ACR criteria for phantom images (34).

The preliminary reader scores are shown in the Table. Except for the tomosynthesis images of a 3-cm mass in a fatty breast, the tomosynthesis images were judged to be superior in lesion visibility, margin visibility, and confidence in classification. In the three subtle lesions, which were in regions of radiographically dense tissue, tomosynthesis images were judged to be diagnostically superior by at least two of the three radiologists for the three parameters. Images of two of the specimens are shown in Figures 8 and 9.

Figure 8 shows tomosynthesis and standard screen-film images of mastectomy specimen 1 (Table), which contained a mass with associated calcifications distributed over a 3-cm^2 area. The tomosynthesis images were reconstructed from seven projections obtained from −15° to +15° in increments of 5°. The total mean glandular radiation dose for acquisition of all of the tomosynthesis images was 1.06 times the radiation dose for acquisition of a single-view, screen-film mammogram. As indicated in the Table, the mass is difficult to detect on the conventional image (Fig 8a). However, the mass is clearly demonstrated

Preliminary Reader Study: Tomosynthesis versus Conventional Imaging of Mastectomy Specimens

Specimen Number	Lesion Description	X-ray–Source Arc	Tomographic Dose/ Conventional Dose*	Parameter	Conventional Imaging Diagnostically Superior	Conventional Imaging Superior	Conventional and Tomosynthesis Imaging Equal	Tomosynthesis Imaging Superior	Tomosynthesis Imaging Diagnostically Superior
1	Subtle irregular mass	30°	1.06	Lesion visibility	–	–	–	+	++
				Lesion margin visibility	–	–	–	–	+++
				Confidence in lesion classification	–	–	–	+	++
2	Subtle calcification cluster	40°	1.05	Lesion visibility	–	–	–	+	++
				Lesion margin visibility	–	–	–	+	+
				Confidence in lesion classification	–	–	–	+	++
3	Subtle rounded mass	40°	0.89	Lesion visibility	–	–	–	+	++
				Lesion margin visibility	–	–	–	–	+++
				Confidence in lesion classification	–	–	–	+	++
	Rounded mass	40°	0.89	Lesion visibility	–	–	+	++	–
				Lesion margin visibility	–	–	–	+	++
				Confidence in lesion classification	–	–	–	+	++
	Architectural distortion	40°	0.89	Lesion visibility	–	–	–	–	+++
				Lesion margin visibility	–	–	–	–	+++
				Confidence in lesion classification	–	–	–	–	+++
4	3-cm mass with irregular margins	30°	1.74	Lesion visibility	–	–	+++	–	–
				Lesion margin visibility	–	+	+	+	–
				Confidence in lesion classification	–	–	+++	–	–

Note.—Scores are for three readers; each individual score is marked by a "+." A "–" indicates that there is no score. One reader did not score the margin visibility of the calcification cluster.

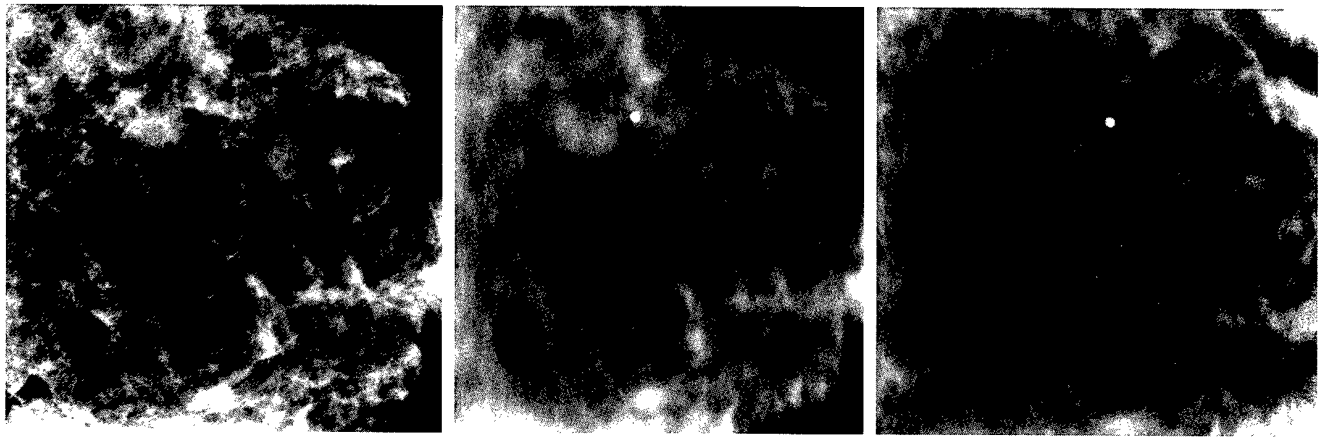
* The ratio of the mean glandular radiation dose for tomosynthesis (sum of the doses from all projections) to that for conventional imaging.

a. b. c.

Figure 8. Images of a mastectomy specimen that contains a subtle mass and associated calcifications. **(a)** Screen-film image obtained at 26 kVp and 197 mAs faintly shows the mass (arrow). **(b)** Tomosynthesis image reconstructed at 7.1 cm above the detector demonstrates the mass (arrow), which was difficult to detect on **a.** Tomosynthesis images were obtained at 5° intervals over a 30° arc. Each image was obtained at 26 kVp and 30 mAs. The total mean glandular radiation dose for acquisition of the tomosynthesis images was approximately equal to the radiation dose for acquisition of one screen-film image in the same specimen. **(c)** Tomosynthesis image reconstructed with the in-focus plane at 6.4 cm above the detector shows a group of microcalcifications (arrow) at this level.

on the tomosynthesis image reconstructed at 7.1 cm above the detector (Fig 8b). The tomosynthesis image reconstructed at 6.4 cm above the detector demonstrates several calcifications at this level (Fig 8c). Figure 8c demonstrates the ability to maintain the contrast and sharpness of small objects in the reconstructed plane wth the algorithms. Figure 8 also demonstrates the ability to determine whether calcifications are associated with a mass and the three-dimensional relationships between masses and calcifications.

Figure 9 shows tomosynthesis images and standard projection digital images of mastectomy specimen 3



a. b. c.

Figure 9. Images of a mastectomy specimen that contains two masses in the upper central regions of the images and an area of architectural distortion in the lower right. **(a)** Conventional digital image obtained at 25 kVp and 100 mAs. **(b)** Tomosynthesis image with the in-focus plane at 4.45 cm above the detector demonstrates two masses and an area of architectural distortion. One of the masses and the area of architectural distortion are better depicted on **b** than on **a**. The tomosynthesis images were obtained at nine positions at −20° to +20° from the detector perpendicular at 5° intervals. Each image was obtained at 25 kVp and 10 mAs. The total mean glandular radiation dose for acquisition of the tomosynthesis images was 0.89 times that for acquisition of the conventional images in the same specimen. **(c)** Same tomosynthesis image as **b** but with self-masking with a kernel that corresponds to 200 pixels (2 cm).

(Table), which contained two masses and an area of architectural distortion. The digital image (Fig 9a) was obtained with conventional imaging geometry by using the same technical parameters as in screen-film imaging. One mass is clearly visible on the conventional digital image; however, the margins are better depicted on the tomosynthesis image (Fig 9b) reconstructed at 4.45 cm above the detector. Another mass slightly above and to the left of the first mass is seen on the tomosynthesis image but not on the conventional image. In addition, a lower-right area of architectural distortion is displayed well on tomosynthesis images but poorly on the conventional image (Fig 9). The total mean glandular dose for tomosynthesis imaging was 0.89 times the dose for conventional imaging. Thus, even at a radiation dose less than the dose for acquisition of a single mammogram, the tomosynthesis images provide improved lesion visibility compared with the lesion visibility on conventional images.

Figure 9c is a self-masking tomosynthesis image obtained at the same level as Figure 9b, at 4.45 cm above the detector, by using a method similar to that of Chakraborty and colleagues (27). In the self-masking tomosynthesis method, a one-dimensional, unsharp mask is used to reduce streaking artifacts. This image demonstrates a reduction in low-frequency noise.

DISCUSSION

For the last 2 decades, efforts to bring tomosynthesis into the clinical environment have been unsuccessful (19–27). These efforts have been hampered by the lack of a digital, flat-panel detector with rapid image readout. Recent advances in detector development have now made clinical application of tomosynthesis possible. Our results indicate that breast tomosynthesis is capable of producing high-quality breast images that may contain information that is currently not visible with conventional imaging.

Phantom studies demonstrate the ability to attain in-focus planes and the ability to depict small microcalcifications. Tomosynthesis images of the ACR phantom, which has no structured noise, demonstrate an image quality comparable with that of conventional images at 1.4 times the radiation dose.

The value of tomosynthesis imaging is evident in images with substantial structured noise from radiographically dense tissue, as demonstrated in the reader study. Although the number of specimens is small, tomosynthesis images of mastectomy specimens demonstrate an improvement in the depiction of lesions. In three of the four specimens, lesions were seen with tomosynthesis that were either not seen or poorly seen with conventional imaging.

The method proposed for tomosynthesis in this study is different from most previous implementations because the images are obtained at discrete tube positions rather than continuously as the tube moves. Consequently, the blurring of structures is not the smooth blurring typical of continuous image acquisition. For example, if nine images are used in the tomosynthesis data set, objects above or below the in-focus plane will be displayed as nine separate objects on the reconstructed image. Each object will have approximately one-ninth the contrast of the original object. For high-contrast objects such as a large calcification, nine images of the calcification may be visible. Although we use the term "blurring," the images of structures outside the in-focus plane are essentially repeated in the direction of x-ray–source motion. High-frequency information is retained, although the contrast of out-of-plane structures is greatly reduced.

Self-masking tomosynthesis (Fig 9c) reduces low-frequency information in the direction of the x-ray–source motion (27). Because of discrete sampling for the proposed method, other image-processing methods may be better suited to reducing the contribution of out-of-focus structures from planes above or below the in-focus plane. A method similar to that of Kolitsi and colleagues (30) will be tested in the future. This method identifies the plane of an out-of-focus structure such as a dense calcification and computes its contribution to all other planes. The image of the structure may then be removed from all planes except for the plane that contains the structure in focus.

There are several potential uses of tomosynthesis for breast imaging. Tomosynthesis may prove to be a valuable screening tool in women with radiographically dense breasts. The ability to see into the middle of the breast by blurring the superimposed structures may

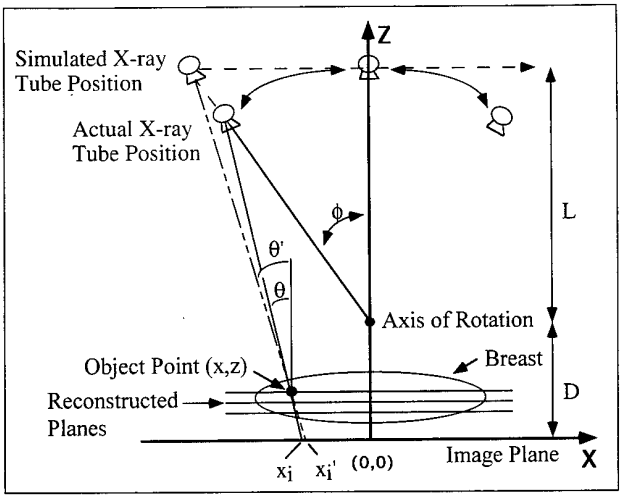


Figure A1. Geometry for tomosynthesis image reconstruction. Diagram defines the angles, distances, and coordinate system used for the reconstruction algorithms. Z = distance above the digital detector.

allow important improvements in the sensitivity of mammographic screening in the early detection of breast cancer. Tomosynthesis may depict cancers in dense breasts or multifocal cancers at a small fraction of the cost of magnetic resonance imaging, which has recently been proposed as another method for detecting these cancers (35).

Tomosynthesis may also be used for problem solving or diagnostic breast imaging. Current mammographic techniques have poor specificity, as 70%–90% of all breast biopsy results are negative (36–38). Tomosynthesis may provide the radiologist with an improved image of a potential lesion. The results shown in the Table indicate that improved depiction of lesion margins may allow the radiologist to have greater confidence in lesion classification and decrease the number of biopsies with benign results. It may also be possible to perform the entire diagnostic evaluation of a lesion with tomosynthesis. Compared with current diagnostic examinations, in which it is necessary to obtain a large number of mammograms, tomosynthesis may save time and reduce patient radiation exposure.

Tomosynthesis will provide three-dimensional information on the dimensions of a lesion, on whether microcalcifications are associated with a mass, and on how they are distributed. The three-dimensional distribution of calcifications is thought to be a useful indicator in discriminating between benign and malignant lesions and thus may also have a positive effect on clinical management (39).

The tomosynthesis method is readily adaptable to current mammographic systems with minor modifications. This geometry has several advantages: (*a*) there are no moving parts near the breast or abdomen; (*b*) existing mammographic machines may be easily altered to allow this type of motion, because many already provide the ability for the tube to move in an arc above the breast; and (*c*) a unit modified for tomosynthesis imaging will still be completely usable for routine breast imaging, which eliminates the need for a dedicated tomosynthesis system. The development of motorized motion of the x-ray tube should allow the acquisition of all of the tomosynthesis images in approximately 3–5 seconds. This is sufficiently rapid to make the system clinically applicable, because these exposure times are similar to exposure times in the acquisition of magnification views with current systems.

In summary, these early results demonstrate that tomosynthesis imaging may be a valuable clinical tool for the early detection of breast cancer and the characterization of benign and malignant lesions.

APPENDIX

The proposed system for breast tomosynthesis imaging is shown in Figure 10. This system requires a different image reconstruction algorithm. As shown in Figure A1, the tomographic angle ϕ is given by the angle of the x rays intersecting the perpendicular to the image plane at the axis of rotation of the x-ray tube. For any given point in the object (x,z), we may define an angle θ as the angle of the x rays intersecting that point relative to the perpendicular to the image plane. The angle θ is a function of ϕ, x, and z, and is given by $\theta(\phi,x,z) = \arctan (L\sin\phi + x)/(L\cos\phi + D - z)$, where L is the distance between the axis of rotation and the x-ray–tube position and D is the distance between the axis of rotation and the image plane (as defined in Fig A1). From this angle, we may derive point x_i, which is the projection of the object point (x,z) onto the image plane:

$$x_i(\phi, x, z) = z(L \sin \phi + x) /(L \cos \phi + D - z). \quad \text{(A1)}$$

$x_i(\phi,x,z)$ is the image point formed by x rays emitted from an x-ray tube that is rotated about the axis. The magnification (M) of points in the object is a function not only of the position z, but also of the angle ϕ: $M(\phi,z) = (L\cos\phi + D)/(L\cos\phi + D - z)$.

Because magnification varies with ϕ and z, it is not possible to reconstruct a tomographic plane by simply shifting and adding the digital images. To facilitate the reconstruction, it is helpful to construct the images that would be produced if the x-ray tube were moved according to the Twinning principle (Fig 1). Thus, if the x-ray tube were rotated by a tomographic angle ϕ, but was constrained to remain in the horizontal plane at a distance of $L + D$ from the image, then the angle of the x rays intersecting an object point would be given as follows:

$$\theta'(\phi, x, z) = \arctan (L\tan \phi + x) /(L + D - z). \quad \text{(A2)}$$

From Equation (A2), it follows that the image point x_i', which is the projection of the object point (x,z) onto the new image plane, is given as follows:

$$x_i'(\phi, x, z) = x + z (L \tan \phi + x) /(L + D - z). \quad \text{(A3)}$$

The proposed x-ray gantry for digital tomosynthesis produces images with image points as defined by Equation (A1). For every x_i in the image, we may use the known value of ϕ and a selected z to determine an object point x with Equation (A1). The values of ϕ, x, and z may then be applied to Equation (A3) to determine a value for x_i' in the new image. The set of new images thus produced may then be used to reconstruct a tomographic plane at z by means of a simple linear shifting process that is analogous to the Twinning method. An example of the method is shown schematically in Figure 5 with projections from tube positions 1–4.

The technique for construction of a new set of images for each desired tomographic plane results in a small distortion of image information for

structures outside the plane. This is because the x-ray paths through the object that occur with rotation of the focal spot about an axis are slightly different from those that occur with movement of the focal spot within a horizontal plane. The magnitude of the distortion increases with the distance from the reconstructed plane and also increases with the distance from the central axis of the image (ie, $x = 0$). The distortion for all points that lie exactly on the reconstructed plane is zero. This off-plane distortion is small compared with the blurring caused by tomography. Because it is our intention to blur the structures above or below the in-focus plane, we do not expect that distortion produced by this technique will have any important effects on the tomographic image quality. The method will allow exact reconstruction of all of the objects in the in-focus plane. ■

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Digital Breast Imaging: Tomosynthesis and Digital Subtraction Mammography

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ABSTRACT: Advances in computer technology and the introduction of new digital imaging detectors offer the potential for digital image acquisition and several new mammography techniques, such as tomosynthesis and digital subtraction mammography.

Tomosynthesis is a method of obtaining tomographic images of a breast. In tomosynthesis, any number of tomographic planes may be reconstructed from a set of images obtained as the X-ray source is moved in an arc above the breast. By shifting and adding the information obtained at different source positions, any plane of the breast can be brought into sharp focus, while structures outside this selected plane are blurred. This may lead to improved lesion detection, especially in dense breast tissue. Thus, tomosynthesis may play a role in improving breast cancer screening and lesion characterization.

Digital subtraction mammography is a method of breast angiography. It is performed by obtaining a digital radiographic image before, and one or more digital radiographic images after, the injection of a contrast agent such as iodine. The pre- and post-contrast images are subtracted, resulting in an image of the vascular structures in the breast. Because breast cancer lesions have increased vascularity, digital subtraction mammography may play an important role in improving lesion detection, characterizing lesions, monitoring response to therapy, and determinating lesion extent.

Thus, both of these new digital techniques have the potential to address the major limitation of conventional mammography, namely the difficulty in detecting cancer in radiographically dense breasts.

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INTRODUCTION

Primarily, mammography does not detect breast cancers because the cancer is masked by normal radiographically dense fibroglandular breast tissues that may be overlying or encompassing the cancer (1–7). Holland et al. found that 76% of missed cancers were in dense breasts (1). The radiographic image of these normal breast structures is referred to as "structured noise." The new digital mammographic techniques, tomosynthesis and digital subtraction mammography, are capable of reducing structured noise in an image; therefore, they offer the potential for improved breast cancer detection.

Film-screen Systems

Current mammographic images are obtained using analog screen-film systems as the image detector. X-rays passing through the breast are absorbed in the phosphor screen,

which emits light. The light from the phosphor exposes the film, which is developed to obtain a mammogram. Screen-film systems have evolved over many years to current systems that have high resolution and high image contrast. Although the image quality obtained with these analog systems is very good, these systems have certain limitations. Current screen-film systems have very high contrast, thus improving the visibility of lesions. However, this high contrast comes at the expense of the dynamic range. As a result, some areas of the image may be presented in the range of film density with high contrast, whereas other areas, such as an area of dense tissue, may be presented at low film density with low image contrast.

Other limitations of screen-film systems include image noise from the film and the film processor, difficulty in obtaining consistent image quality, and the fixed image presentation. Maintaining a consistent image quality for analog screen-film mammography requires constant monitoring and testing, with the film processor being the primary source of instability. Film processors also may add artifacts to the images thus degrading image quality. The film itself may be a source of noise because of the size and distribution of silver halide grains in the film emulsion. In addition, the use of an analog film limits the ability to use digital image processing. Finally, archiving of film requires large storage areas and expensive film library management. If a study is lost, the information is irretrievable.

Digital Detectors

Digital detectors are expected to replace analog film-screen systems because digital detectors address many of the limitations of analog mammography (8–10). Digital detectors are expected to have much wider dynamic range, provide consistency of image quality, eliminate film granularity, and allow post-processing of the image. Although the clinical evaluation of digital mammography systems has only begun recently, many of the benefits of digital imaging have been demonstrated with digital imaging of other organs or regions, such as the chest (11). Additional benefits of digital mammography include the ability to archive the images on tape or optical discs and the ability to transmit images rapidly.

The ability to perform image processing is the primary benefit of digital imaging that will make tomosynthesis and digital subtraction mammography possible. Both tomosynthesis and digital subtraction mammography require mathematical processing of the original images.

TOMOSYNTHESIS

Background

Tomosynthesis is similar to conventional X-ray tomography. Conventional tomography is performed with a single exposure and a single image is generated. On the other hand, tomosynthesis is performed by acquiring multiple images with a digital detector. Like conventional tomography, tomosynthesis may be performed using many different tube motions including linear, circular, elliptical, hypocycloidal, and others. The geometry used for conventional linear tomography is demonstrated in Figure 1. Using this method, all objects are blurred with the exception of those at the fulcrum of the tomographic motion. The blurring of objects above or below the in-focus plane will reduce the "structured noise" from these planes and may provide improved visibility of structures located at the in-focus plane.

Tomosynthesis may be performed with the geometry used at our institution as shown in Figure 2 (12). Multiple images are obtained as the tube moves above the object. Images are acquired using either a step and expose method (the tube is stationary for each exposure and then moves to the next position), or with a continuous exposure method with rapid image readout (multiple images are acquired

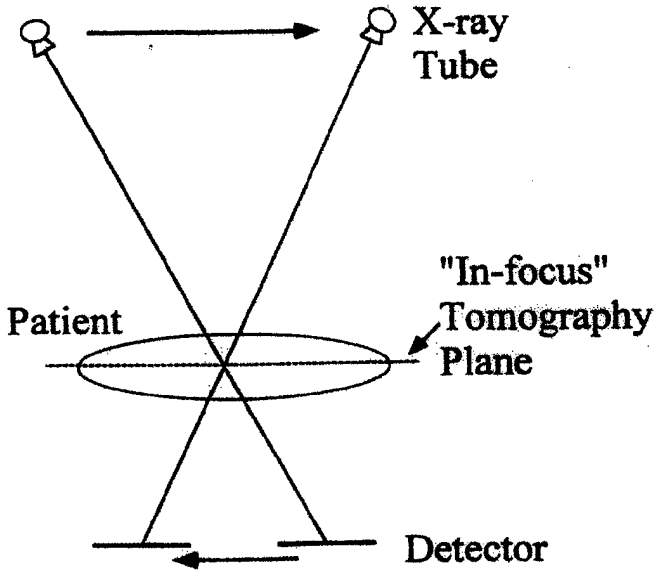

Fig. 1. The Twinning geometry used for conventional linear tomographic imaging. The X-ray source and detector move parallel to the in-focus tomographic plane. The in-focus plane is located at the fulcrum of the motion. (Reprinted with permision from the Radiological Society of North America. From: Niklason LT, Christian BT, Niklason LE, et al. Digital tomosynthesis in breast imaging. Radiology 1997; 205:399–406).

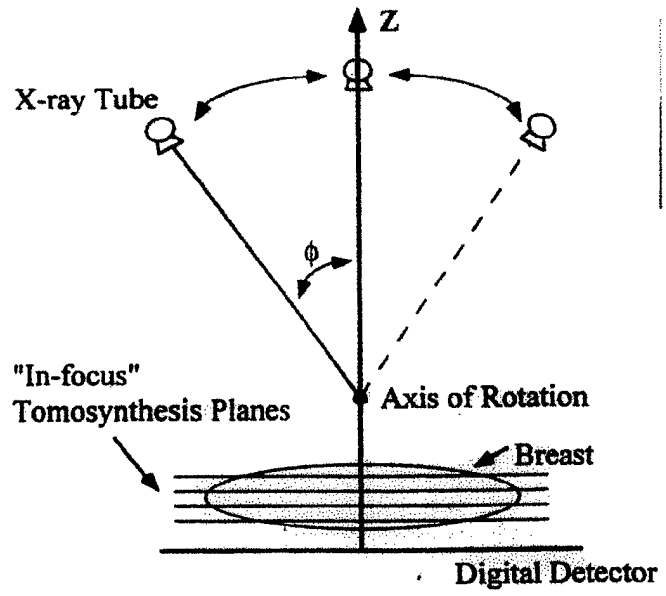

Fig. 2. A geometry for breast tomosynthesis. The X-ray source moves in an arc above the breast. The X-ray source is stationary during each X-ray exposure and is then moved along the arc to the next position. The number of positions is variable. The breast and digital detector remain stationary. (Reprinted with permision from the Radiological Society of North America. From: Niklason LT, Christian BT, Niklason LE, et al. Digital tomosynthesis in breast imaging. Radiology 1997; 205:399–406).

as the tube moves). By shifting and adding the digital images thus obtained, it is possible to reconstruct *any* plane in the breast that is parallel to the detector (13–16). Other structures outside of the in-focus plane are blurred because they are misregistered.

Tomosynthesis has several advantages over conventional tomography. First, tomosynthesis has an important radiation dose advantage, since all of the images comprising one study are obtained with a total dose approximately equal to one conventional mammogram (single view). In contrast, using conventional tomography to image an average breast with a compressed breast thickness of 4.5 cm would require 15 tomograms, each with a radiation dose similar to a single mammogram, to display the entire breast if the in-focus plane width were 3 mm. Therefore, conventional tomography would require approximately 15 times more radiation dose than tomosynthesis for a breast of average thickness.

Second, digital image processing can be applied to improve tomosynthetic image quality. One method to reduce artifacts from out-of-focus structures utilizes a one dimensional unsharp masking technique called self-masking tomosynthesis (17–19). Additional methods to reduce the contribution of out-of-focus structures in the in-focus plane have also been reported (20–22). These techniques may produce tomosynthetic images that are substantially better than conventional tomography images.

Researchers have attempted to use tomosynthesis for clinical X-ray imaging for the past two decades (14–19,23–30). These efforts have used several detector systems and involved imaging for a wide range of exams. Unfortunately, the image detectors have limited the success of these previous attempts at digital tomosynthesis.

Methodology

For breast tomosynthesis, seven to nine projection images may be obtained, each at a low radiation dose; therefore, the total dose from all projection images comprising one study is equal to or slightly higher than the radiation dose from a single view mammogram. After data acquisition is complete, the images are reconstructed using a method outlined in Figure 3. An initial in-focus plane is chosen for the reconstruction, and the correct image shifts are calculated to reconstruct a tomogram at the chosen height above the detector. By shifting the images only the plane of interest remains registered in all images, effectively blurring the remaining planes due to misregistration. This process is repeated for each selected in-focus plane of the breast such that all of the breast is shown in sharp focus on at least one tomogram. The images may then be viewed either by printing each plane on a film or using a computer workstation display system. The reconstruction algorithms are described in detail by Niklason et al. (12).

The tomosynthesis method is adaptable to current mammography systems with minor modifications. Existing mammography systems allow the motion of the X-ray tube in an arc relative to the detector. This motion has been used for obtaining stereo image pairs but may be modified to obtain tomosynthesis images. It is not necessary to build a separate unit to perform tomosynthesis since the same unit would be usable for conventional mammography.

Results

The major benefit of tomosynthesis is conferred by its ability to reduce structured noise, allowing improved visualization of internal breast structures and lesions. Figure 4 shows conventional (a) and tomosynthesis (b) images of a region of a mastectomy specimen. This region of the specimen contains a mass and an area of architectural distortion with a radial spiculated pattern. The tomosynthesis image shown in Figure 4 (b) demonstrates the mass margins better and also demonstrates the architectural distortion better than the conventional image. In this case, the total radiation

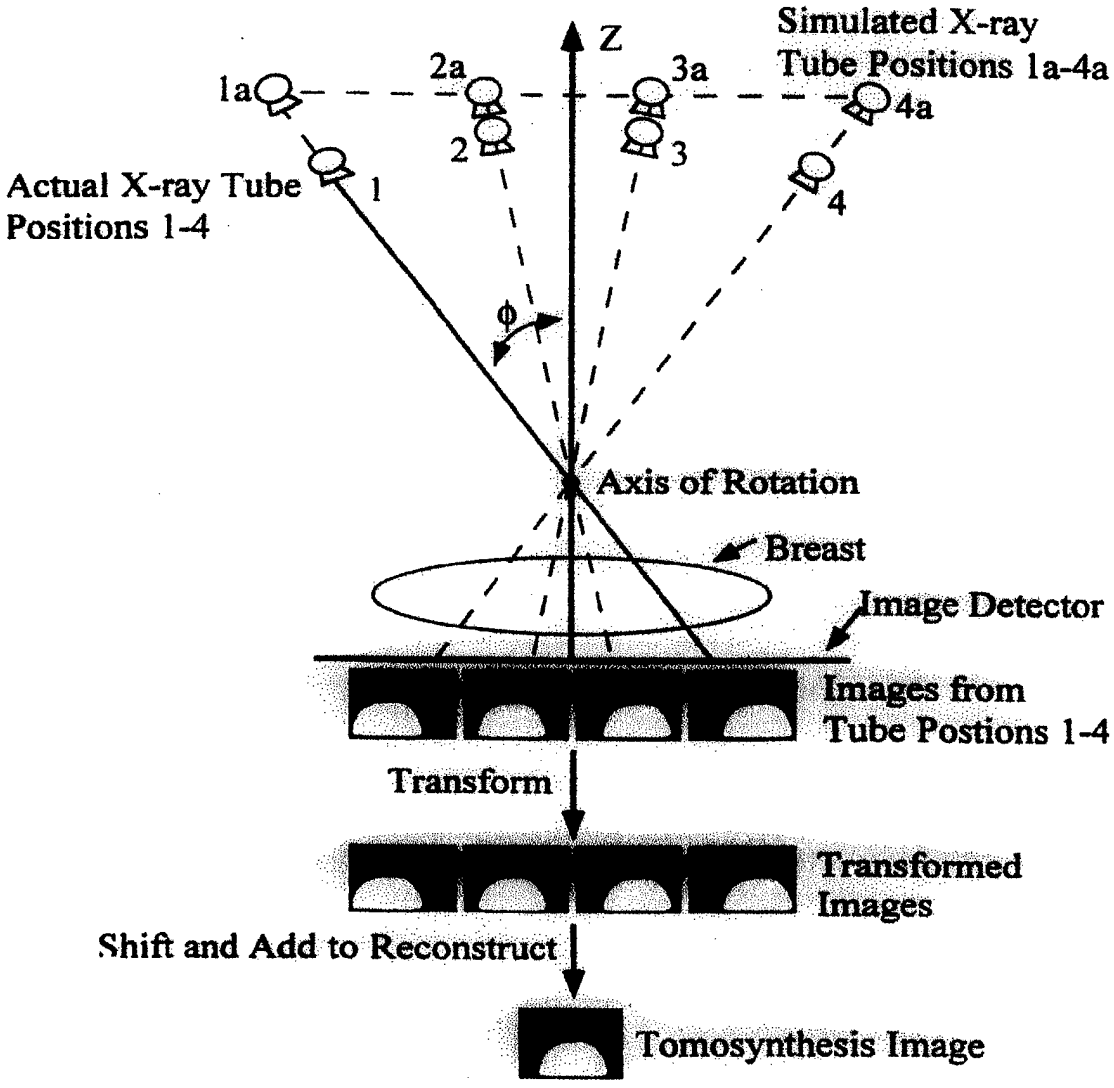

Fig. 3. A diagram of the tomosynthesis reconstruction method showing four X-ray tube positions. Only four X-ray tube positions are shown for simplicity, typically more source positions would be used. Images are obtained from the four positions labeled 1–4. These images are transformed to construct images that would be obtained from source positions 1a–4a. After transformation these images are shifted and combined to create a tomosynthesis image at any level in the breast. (Reprinted with permision from the Radiological Society of North America. From: Niklason LT, Christian BT, Niklason LE, et al. Digital tomosynthesis in breast imaging. Radiology 1997; 205:399–406).

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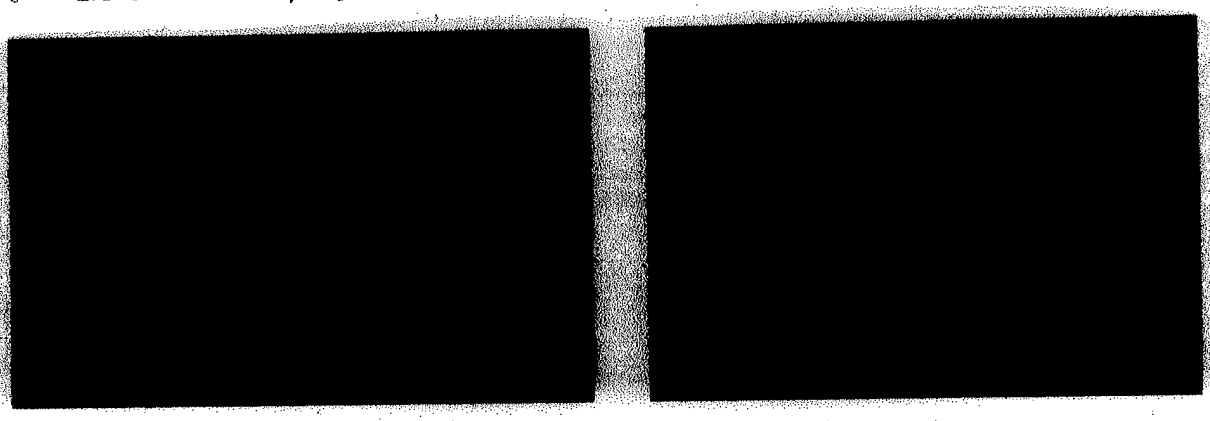

Fig. 4. Images of a mastectomy specimen containing a mass on the left and an area of architectural distortion in center right region of the image.
(a) Conventional digital image of the mastectomy specimen.
(b) Tomosynthesis image with the in-focus plane at a level of 4.45 cm above the detector, demonstrates the mass and an area of architectural distortion with a radial spiculated appearance.

dose for the tomosynthesis images was 11% less than that from the single conventional image. Thus, even at a radiation dose less than a single mammogram, the tomosynthesis images provide improved lesion visibility compared to conventional techniques.

Figure 5 demonstrates another specimen image of a large mass in a relatively fatty breast. This mass was easily detected without tomosynthesis, however, close inspection of the tomosynthesis image does reveal improved imaging of structures, such as the Copper's ligaments.

Phantom images of the American College of Radiology breast phantom and others demonstrate the ability of tomosynthesis to display small calcifications, masses, and simulated spiculations at a level sufficient to pass the accreditation process for mammography devices and at a radiation dose below the accreditation limits (12).

Tomosynthesis provides a series of tomograms encompassing the entire breast, with each image displaying only one plane of the breast in sharp focus. The thickness of the in-focus region displayed in sharp focus is dependent on the total angle of X-ray tube travel. For example, if the X-ray tube is moved through a 40 degree arc, the in-focus plane thickness would be approximately 2.5 mm. If the tube travels through a smaller arc, objects above or below the plane are less blurred, and the thickness of the in-focus plane is increased. For a 10 degree X-ray tube arc, the in-focus plane thickness increases to approximately 10 mm.

Experiments to date have been limited to phantoms and specimens because the X-ray source is moved manually. The fast acquisition times required for clinical imaging will require a motorized X-ray source motion. The development of motorized X-ray tube motion may allow the acquisition of all projection images in approximately three to five seconds (a single breath hold). This may be sufficiently rapid to make the system clinically applicable, since these exposure times are similar to magnification views with current systems.

Discussion

The major conclusions from previous phantom and specimen imaging (12) include:

(a) tomosynthesis may be performed at a low radiation dose similar to conventional mammography;
(b) tomosynthesis improves the visibility of a lesion and its margins and increases the confidence in lesion classification; and
(c) the new generation of digital detectors will make breast tomosynthesis practical.

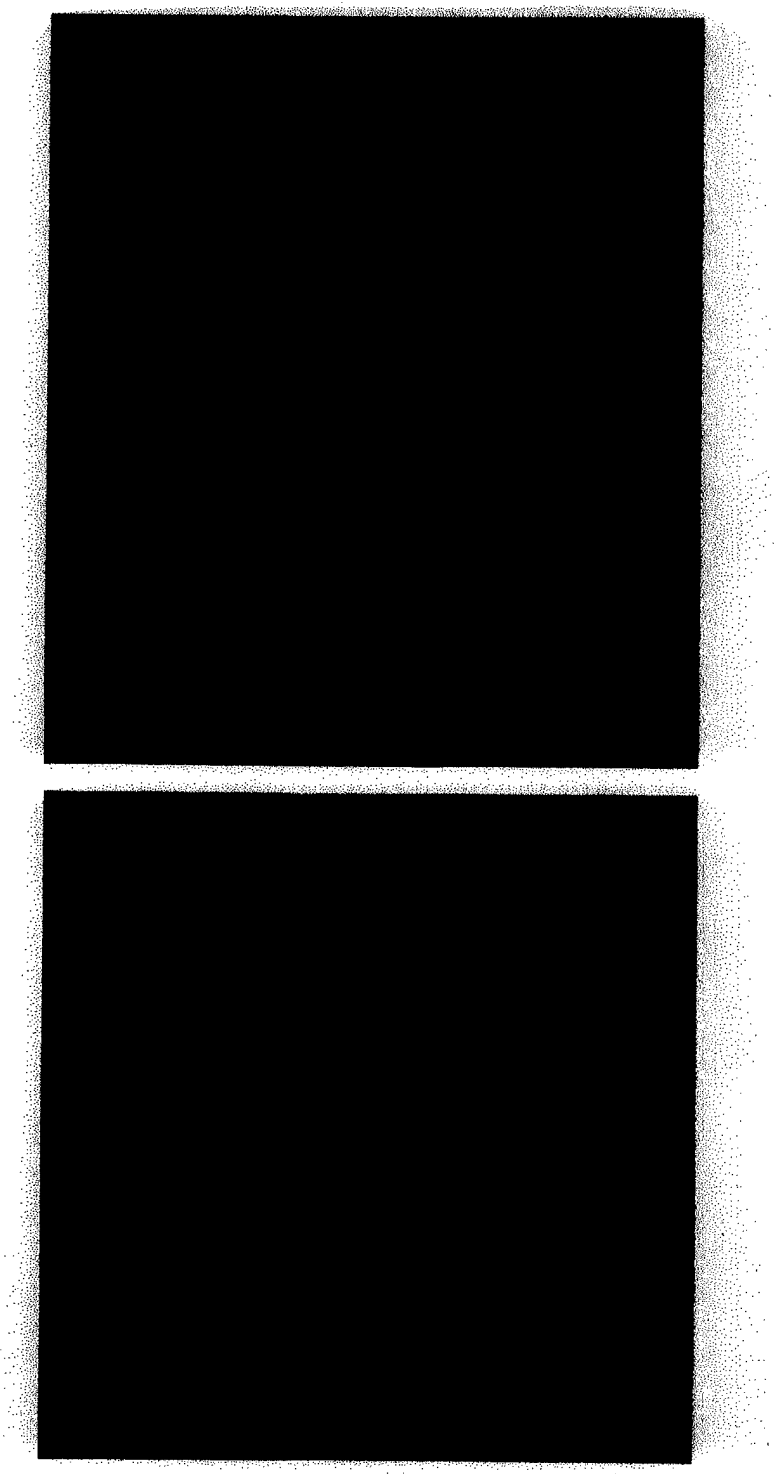

Fig. 5. (a) A conventional projection image of a mastectomy specimen with a large 3 cm mass.
(b) Tomosynthesis image reconstructed at the level of the center of the mass. The mass is easily seen in the conventional view, however, some structures such as the ligaments are better visualized using tomosynthesis.

Tomosynthesis may be useful as a screening device and as an aid in problem solving mammography. As a screening device, tomosynthesis may prove to be a valuable tool for women with radiographically dense breasts. The ability to "see into the middle of the breast" by blurring the superimposed structures will potentially allow significant improvements in the sensitivity of mammography screening.

Many women are recalled for further evaluation because superimposed normal tissues may appear suspicious. Using tomosynthesis for the screening exam may avoid recall for this group of women, since the tomosynthesis images may facilitate differentiation of a lesion from superimposed tissue.

In problem solving mammography, it may be possible to perform the entire evaluation of a lesion with tomosynthesis, thus reducing the total radiation exposure compared to a standard diagnostic examination, which may involve many mammograms. Current mammographic techniques have poor specificity, since 70–90% of all breast biopsies are negative (31–33). Tomosynthesis may provide the radiologist with an improved image of a potential lesion by blurring the structures above and below the lesion. This may allow the radiologist to have improved confidence in lesion classification that may lead to a decreased number of negative biopsies. The improved visualization of lesion borders may also reveal spiculations that are characteristic of malignant lesions. Moreover, as tomosynthesis is a volumetric imaging technique, it provides information about the dimensions of a lesion, whether microcalcifications are associated with a mass, and how they are distributed. This is important since the three-dimensional distribution of calcifications is thought to be a useful indicator in discriminating benign versus malignant lesions (34). Tomosynthesis has the potential to detect multifocal cancer during the problem solving evaluation of a lesion at a small fraction of the cost of magnetic resonance imaging, which recently has been proposed as a method of detecting multifocal breast cancer (35).

Tomosynthesis may be performed with less compression than conventional mammography because it is not critical to spread the breast structures parallel to the detector. Actually, the structures above and below the plane of interest are more blurred (thus, it is easier to see through these structures) when less compression is used. Less compression results in increased patient comfort and compliance, which is important as breast compression is a major source of complaints in mammography and may reduce screening frequency and compliance. However, some compression is still needed to hold the breast stationary and to reduce the breast thickness in order to minimize the radiation dose.

Research Directions For Future Development

To date, work on breast tomosynthesis, although preliminary, has been encouraging. Future studies needed to develop tomosynthesis into a routine, clinical tool include:

- Further phantom and specimen studies to optimize the imaging parameters.
- Motorization of X-ray source to allow rapid image acquisition.
- Image processing and display development.
- A clinical comparison of digital imaging versus digital tomosynthesis.

DIGITAL SUBTRACTION MAMMOGRAPHY

Background

Breast tumor growth is strongly dependent on angiogenesis and adequate delivery of nutrients. For increases to occur in the tumor cell population, an increase in new capillary growth must also occur to provide a sufficient delivery of glucose and oxygen for cell proliferation (36). The increased vessel density, as compared to the adjacent normal tissue, may provide a method for detecting early

stage cancers. In non-small cell lung cancer, Macchiarini et al. (37) have shown that the microvessel density count, the best method currently available for the assessment of angiogenesis, is a major predictor of metastasis. They also show that angiogenesis significantly correlates with late treatment failure due to metastases that occur at a critical microvessel density in the tumor (38). Angiogenesis and tumor vascularity also play a relevant role in the biologic aggressiveness of early breast cancer, and patients with highly vascularized tumors have been shown to be at higher risk of tumor recurrence (39). Moreover, evidence shows that tumor vascular physiology is demonstrably different from that seen in normal breast tissue (40–42). Contrast agent uptake rate has been shown to correlate with the microvessel density in a tumor (41,43) and to be higher in malignant tumors than in benign lesions (42,44). However, a significant overlap has been demonstrated, reducing the value of this parameter in distinguishing between these possibilities (43,44). Buadu et al. have suggested that a combination of anatomical and physiological features may lead to improved diagnosis of breast cancer (43).

Digital subtraction angiography of the breast is a method of imaging a tumor's vascular morphology. We will refer to digital subtraction angiography of the breast as digital subtraction mammography (DSM). Digital subtraction mammography may have a role in:

(a) early detection of breast cancer,
(b) improved differentiation of benign from malignant lesions,
(c) determination of the aggressiveness of a tumor by assessing the microvessel density,
(d) improved determination of cancer extent by identifying the area of increased vascularity, and
(e) monitoring the effectiveness of therapy.

Conventional mammography allows detection of many cancers in the 5–8 mm range (32,35), although even larger cancers may be difficult to detect in radiographically dense tissues.

Methodology

Digital subtraction mammography is performed by obtaining a mask image before and one or more iodine images after or during injection of contrast. The mask image is subtracted from each of the iodine images to remove all of the normal anatomy and obtain an image of the vasculature. The subtraction process removes the structured background that may reduce cancer detection in conventional mammography. DSM was applied to breast imaging by Watt et al. (45) in the early 1980s. Watt and colleagues were successful in demonstrating differences between tumor and normal breast tissue; however, the method was not widely used because of the low spatial resolution and spatial distortion resulting from the use of an image intensifier. Digital detectors with high resolution, minimal distortion and rapid image readout have been developed which may make breast DSM practical.

Results

We have investigated a digital mammography imaging system (General Electric, Milwaukee, WI) as a potential system for breast DSM. Silicon and silica tubing with inner lumen diameter of 0.049 to 0.76 mm was placed on a 5 cm breast equivalent material (BR12) approximating 50% fat/50% glandular breast tissue. Images were obtained with the tubing filled with saline and then with an iodine concentration of 40 mg/cm^3. Figure 6 demonstrates DSM images of this phantom using the digital mammography system (a), and a state-of-the-art neuroangiography equipment (b) (Toshiba Medical Systems, Tustin, CA). The latter image was obtained to compare the capabilities of a state-of-the-art angiography room to that of the new flat panel mammography detectors. Clearly, the new detectors are capable of displaying vessels with a 150 micron inner lumen while state of the art angiography equipment may display vessels between 250 to 375 micron inner lumen.

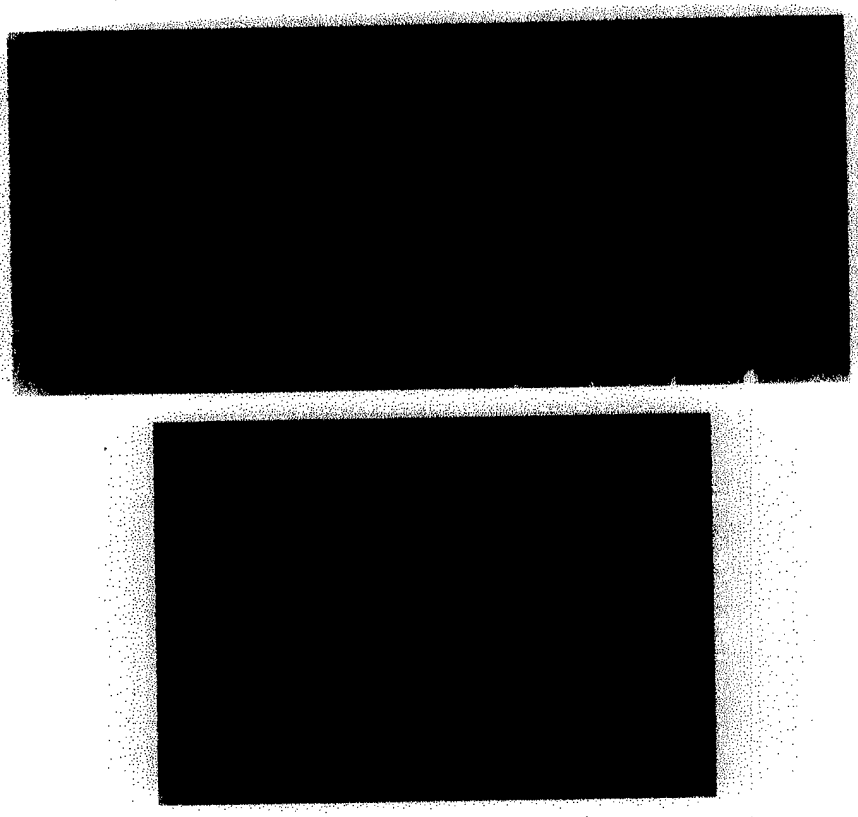

Fig. 6. Images of a phantom composed of 5 cm of breast equivalent material, with tubes from 49 to 760 microns in inner lumen diameter. The tubes are filled first with saline and then with 40mg/cm^3 of iodine.
(a) A digital subtraction mammogram of the phantom obtained using 45 kVp, 0.3 mm focal spot size, 15 mAs, Rhodium target and Rhodium filter.
(b) A digital subtraction angiogram obtained from a state-of-the-art neuroangiography room. This image was obtained at 60 kVp, with a Tungsten target, Aluminum filtration, six inch field of view, five mAs, 0.3 mm focal spot and a magnification of 1.5.

Figure 7 demonstrates a DSM image of a VX2 tumor implanted in the leg of a rabbit. VX2 carcinoma is an anaplastic squamous cell tumor that results from a malignant change of a Shope virus-induced skin papilloma of the domestic rabbit and demonstrates high angiogenic capacity (46). In Figure 7 (a), which is an image obtained before contrast material has arrived, the tumor is not seen. Figure 7 (b) was obtained 10 seconds after a venous injection of contrast and clearly demonstrates the small vessels surrounding the tumor. Finally, Figure 7 (c) is a DSM image obtained by subtracting an image obtained 30 seconds after injection from the mask image obtained prior to the injection of contrast. In this subtraction image, a highly vascularized tumor is seen clearly.

The initial phantom and animal studies have demonstrated the ability of a digital mammography system to demonstrate tumor vessels of the order of 0.15 mm which are much smaller than seen with any other current imaging modality. The images of a VX2 tumor in rabbit also demonstrate the ability of DSM to display a cancer lesion that is not visible using conventional radiography.

Discussion

Digital subtraction mammography has a potential for detecting cancers earlier than anatomical techniques. Since a tumor must recruit new microvasculature to grow, it may

Fig. 7. Images of a rabbit leg containing a VX2 tumor of approximately one cm in diameter.
(a) An image of the tumor prior to contrast injection.
(b) An image obtained approximately 10 seconds after an intravenous injection of iodine contrast.
(c) A digital subtraction mammogram obtained by subtracting an iodine image obtained approximately 30 seconds after injection from the mask image shown in (a).

be possible to find small cancer of less than 5 mm in diameter. However, it will be necessary to perform clinical studies to determine at what size an area of increased vascularity may be called suspicious and differentiated from normal breast vasculature. The ability to find early cancers may initially have a role in high-risk populations. Two groups that may benefit would be women with a genetic predisposition to breast cancer, and women who have undergone breast cancer therapy.

The digital mammography system offers an advantage of much higher spatial resolution than CT or MRI, which have also been used to assess tumor vascularity. In addition, DSM will require much less radiation dose than CT and will cost significantly less than MRI. For detection, breast DSM may require only two mammograms, pre- and post-contrast, which would require a radiation dose of approximately two mammograms.

The early studies involving contrast enhancement using either MRI or DSM have indicated some overlap in the enhancement patterns of benign and malignant lesions (43,45). However, Buadu et al. (43) have suggested that the combination of morphology and dynamic enhancement may allow the differentiation. Digital mammography will be capable of showing the lesion morphology and it will be possible to image rapidly and with high resolution the enhancement pattern during contrast kinetics in a tumor. In MRI imaging there is a tradeoff between the imaging speed and the resolution. For small voxels on the order of a cubic millimeter, it is currently not possible to image rapidly enough to get an adequate measurement of the dynamics of tumor enhancement. The radiation dose and large field of view limit the usefulness of CT for breast imaging.

Current mammographic and pathologic methods have difficulty in determining the extent of a breast cancer. Treatment depends upon surgical excision of the bulk of the tumor, and external radiation is used to destroy any tumor remaining. The surgeon is often unable to determine the extent of the cancer during excision, and the pathologist samples only a small fraction of the excised tissue. As a result, DSM, which will image the tumor vasculature, may improve the ability to identify the tumor margins and may assure a more complete excision of the tumor. Identifying the tumor extent could potentially reduce local cancer recurrence and save lives.

Radiation, chemical, or angiogenesis inhibitor therapy may alter the tumor vascular structure and function. Digital subtraction mammography provides a tool for monitoring a therapy that is targeted to vasculature and may provide an early indication of treatment success. Therefore, using DSM has the potential to tell if a therapy is working and to allow adjustments in both the type and dosage of therapy without having to wait for a change in tumor size.

Research Directions For Future Development

The investigation of breast DSM has just begun. The work needed to test the clinical efficacy of the technique includes:

- Evaluation of the clinical benefits of DSM for breast cancer detection, initial experiments may be on high-risk groups.
- Functional measurements of tumor vascularity to determine tumor perfusion, in addition to morphological measurements.
- Determination of whether differentiation between benign and malignant lesions is possible using DSM.
- Determination of the usefulness of DSM in monitoring therapy.
- Evaluation of the effects of compression on DSM.

SUMMARY

Tomosynthesis and digital subtraction mammography address the major limitation of current mammography imaging methods, namely

the difficulty of finding cancer in radiographically dense breast tissue. Both techniques are capable of reducing structured noise for normal breast anatomy to allow improved visualization of cancer. Tomosynthesis reduces structured noise by blurring structures above or below the plane of interest. Digital subtraction mammography reduces structured noise by subtraction of normal breast anatomy, resulting in an image of breast vasculature. In fact, it may be possible to combine the two methods to offer further improvement (25). Tomosynthesis and breast DSM may offer some of the major benefits in the change from analog to digital breast imaging.

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